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Erythema & Telangiectasia

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Erythema Multiforme



- A self-limited but potentially recurrent disease.
- Abrupt onset of papular "target" lesions, with the vast majority of lesions appearing within 24 hours.
- Two types of target lesions are recognized: (1) Typical, with at least three different zones; and (2) atypical papular, with only two different zones and/or a poorly defined border.
- Target lesions favor acrofacial sites.
- Erythema multiforme minor: Typical &/or occasionally atypical papular target lesions with little or no mucosal involvement and no systemic symptoms.
- Erythema multiforme major: Typical and/or occasionally atypical papular target lesions with severe mucosal involvement and systemic features.
- A preceding HSV infection is the most common precipitating factor; occasionally, there are other preceding infections or, rarely, drug exposure.
- Diagnosis of erythema multiforme requires clinicopathologic correlation and is not based solely on histologic findings.
- Erythema multiforme does not carry the risk of progressing to toxic epidermal necrolysis.



Erythema

It is redness of the skin that blanches under pressure of a finger. It is due to an increase in blood flow within subpapillary plexus or to an increased visibility due to changes in adjacent tissues.

There are four main groups of erythema:

1. **Diffuse erythematous eruptions:** Due to drug sensitivity, virus exanthems, streptococcal infection or systemic disease, e.g. LE or lymphoma.
2. **Localized erythematous eruptions:** Due to trauma, heat, chemical irritants, light or cold, drug eruption.
3. **Reticulated erythema:** e.g. cutaneous polyarteritis nodosa.
4. **Figurate erythema:** Annular, arciform or polycyclic.

Palmar erythema

- With other skin diseases, e.g. eczema, psoriasis, PRP, tinea and many genodermatoses.
- Pregnancy and liver disease.
- With systemic diseases, e.g. SLE, rheumatoid arthritis.
- Idiopathic.

Erythema multiforme "EM"²

It is an acute, self-limited, mucocutaneous syndrome with marked tendency to recurrences.

Age: Predominantly in young adults and is very uncommon during childhood.

Sex: More in males.

Etiology and pathogenesis

- In 50% of the cases, the cause is unknown. An immunological mechanisms are usually present. IF studies demonstrate IgM & C3 in the walls of superficial dermal vessels, in lesions less than 24 hours old. Circulating immune complexes have been demonstrated.
- Autoantibodies against epithelial cells or against desmoplakin have been demonstrated.
- There is association with HLA-DQw3, DRw53 & Aw33.

What are target lesions?

Causes of erythema multiforme

- **Infections:** Approx. 90% of cases:
 - Virus: H. simplex*, vaccinia, AIDS, hepatitis B, Orf, Milker's nodules.
 - Mycoplasma pneumoniae**, histoplasmosis.
 - Mycobacteria, e.g. TB, leprosy.
- **Drugs:** e.g. sulfonamides, sulphones, contraceptive pills.
- **Autoimmune & vascular disease,** e.g. LE, DM, polyarteritis nodosa, Wegener's granulomatosis.
- **Malignancies,** e.g. carcinoma, leukemia.
- **Pregnancy, autoimmune progesterone dermatitis.**
- **X-ray therapy, sarcoidosis, contact reactions.**
- **Idiopathic.**

* The most common causes.

**Also precipitating factor for Stevens-Johnson syndrome & isolated oral mucositis.

Clinical features

1. **EM minor** (Figs 1-11): It is the commoner mild form. There is an acute (about 7-10 days duration), bilateral & symmetrical eruptions of multiforme lesions, i.e. macules, papules, urticaria, & vesicles, with the characteristic iris or target lesions. Target lesions typically consist of three zones. The first zone consists of a dark or blistered center (bull's-eye) that is surrounded by a second, pale zone. The third zone consists of a rim of erythema. Target lesions classically are found on the palms of a patient with erythema multiforme. The lesions appear in successive crops each fade in 1-2 weeks. The extremities (especially palms, soles) and face are commonly affected. Erosions of oral mucous membranes may occur rarely.

Recurrent EM minor is usually associated with HS preceding it by several days. Acyclovir therapy prevents recurrence of herpes as well as EM.

Types of target lesions

- **Typical target lesions:** Papular, well-defined, with at least 3 different zones.
- **Atypical target lesions:**
 - Papular but with only two zones &/or a poorly defined border.
 - Flat (macular) with only two zones &/or a poorly defined border, as well as being non-palpable. They are seen in SJS or TEN, but not EM.



Fig. 1. EM minor



Fig. 2. EM minor



Fig. 3. EM minor

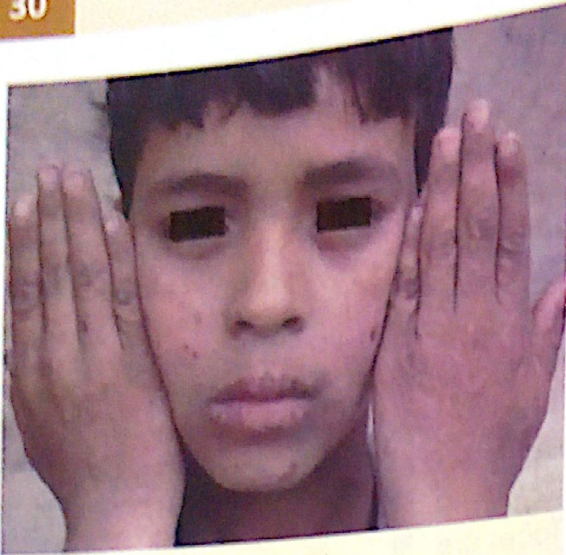


Fig. 4. EM minor



Fig. 5. EM minor



Fig. 6. EM minor



Fig. 7. EM minor



Fig. 8. EM minor



Fig. 9. EM minor



Fig. 10. EM minor



Fig. 11. EM minor

2. **EM major** (Figs 12-14): A severe form.

There is high fever, malaise and arthralgia. Generalized bullous & maculopapular lesions (with a tendency to become confluent) occur with affection of oral mucous membranes in all cases in the form of extensive bullae formation followed by erosions. New crops of lesions develop over a period of 3-4 weeks.

Many organs may be affected: Severe catarrhal or purulent conjunctivitis, genital mucosa, pneumonitis and renal affection. Death may occur in 5-15% of untreated cases.



Fig. 12. EM major



Fig. 13. EM major

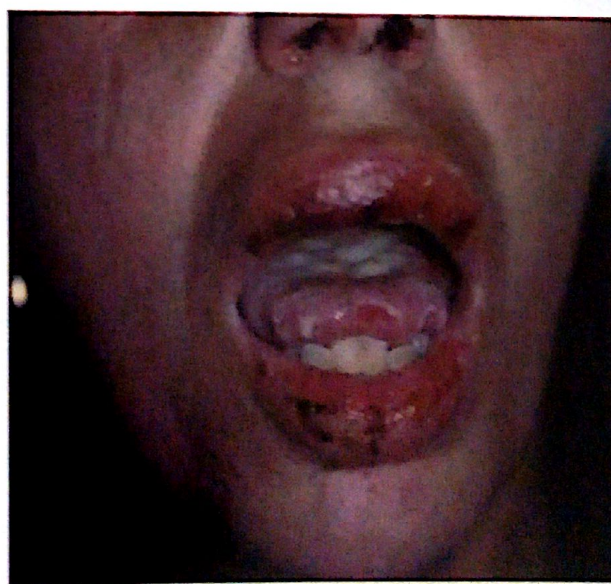


Fig. 14. EM major

NB: Erythema multiforme does not carry the risk of progressing to toxic epidermal necrolysis.

	EM minor	EM major
Type of skin lesions	• Typical targets • $\pm$ Papular atypical targets	• Typical targets • $\pm$ Papular atypical targets • Occasionally bullous lesions
Distribution	Extremities (especially elbows, knees, wrists, hands), face	Extremities, face
Mucosal involvement	Absent or mild	Severe
Systemic symptoms	Absent	Present
Progression to TEN	No	
Precipitating factors	• Herpes simplex virus • Other infectious agents	• Herpes simplex virus • Mycoplasma pneumonia • Other infectious agents • Rarely, drugs

Histopathology (Figs 15, 16)

- **Epidermal changes:** Include focal eosinophilic necrosis of keratinocytes, spongiosis, & vacuolar degeneration of basal cells that may produce subepidermal bulla with basement membrane in the floor of bulla.
- **Dermal changes:** Include perivascular mononuclear cell infiltrate, edema of upper dermis and extravasation of RBCs.

Diagnostic criteria of EM

- Skin &/or MM affection.
- Acute onset & self-limited or episodic course.
- Duration must be less than 6 months "for each episode".
- Typical & fixed skin lesions >7 days.
- Target lesions.

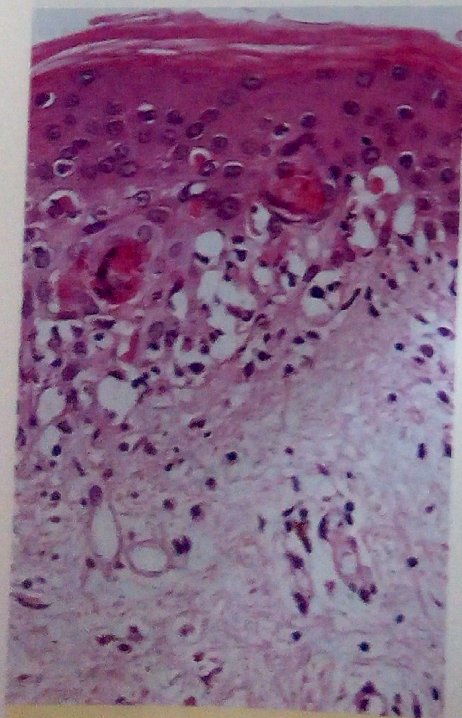


Fig. 15. Histopathology of EM

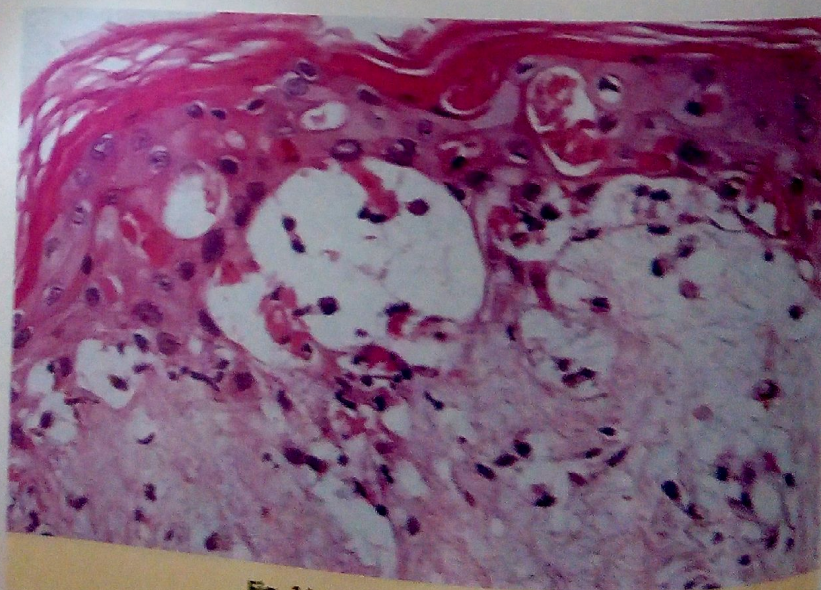


Fig. 16. Histopathology of EM

Differential diagnosis

• **Erythema multiforme differs from bullous pemphigoid by:**

- Eosinophils, if present, are perivascular and not near epidermis.
- Cells near DEJ are mononuclear rather than eosinophils.
- Prominent epidermal changes.

• **Urticaria:**

Urticaria	Erythema multiforme
Central zone is normal skin	Central zone is damaged skin (dusky, bullous or crusted)
Lesions are transient, lasting less than 24 hours	Lesions "fixed" for at least 7 days
New lesions appear daily	All lesions appear within first 72 hours
Associated with swelling of face, hands or feet (angioedema)	No edema

Adapted from: Bologna et al., *Dermatology Textbook*, third edition, 2012.

Treatment

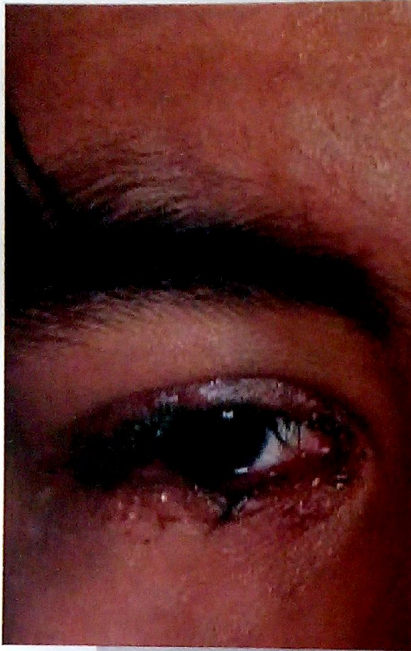
1. **Prophylactic treatment of recurrent disease:**

- **In HSV-associated EM with frequent recurrences, prophylaxis for at least 6 months with:**
 - Oral acyclovir (10 mg/kg/day in divided doses), or
 - Valacyclovir (500-1000 mg/day, with dose depending upon frequency of recurrences), or
 - Famciclovir (250 mg twice daily).
- **If resistant to prophylactic antiviral therapy:** Azathioprine (100 mg/day for several months), prednisone (0.5 mg/kg/day for several months), thalidomide, dapsone, cyclosporine, mycophenolate mofetil and PUVA. Pulse methylprednisolone (20 mg/kg/day for 3 days) can be used in severe forms of EM with functional impairment.

2. **Treatment of the acute eruption:**

- Treatment of the underlying cause, if possible.
- Systemic antibiotics to guard against 2ry infections.
- Minor cases require only symptomatic treatment.
- Major cases may require systemic steroids: 30-60 mg prednisone daily (0.5-1 mg/kg/day), decreasing over a period of 2-4 weeks.

Stevens-Johnson Syndrome & Toxic Epidermal Necrolysis



- Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are two rare, potentially fatal, adverse cutaneous drug reactions of differing severity, characterized by mucocutaneous tenderness and erythema as well as extensive exfoliation.
- SJS is characterized by <10% body surface area of epidermal detachment, SJS-TEN overlap by 10-30%, and TEN by >30%.
- The medications most frequently incriminated are allopurinol, nonsteroidal anti-inflammatory drugs, antibiotics and anticonvulsants. TEN and SJS usually occur 7-21 days after initiation of the responsible drug.
- The average mortality rate is 1-5% for SJS and 25-35% for TEN; it can be even higher in elderly patients and in those TEN patients with a very large surface area of epidermal detachment.
- Exfoliation is due to extensive death of keratinocytes via apoptosis; the latter is mediated via the cytotoxic secretory protein granulysin and interaction of the death receptor-ligand pair Fas-FasL.
- Optimal medical management of SJS and TEN requires early diagnosis, immediate discontinuation of the causative drug(s), & rapid initiation of supportive care and specific therapy.
- Specific therapies that have the potential to selectively block keratinocyte apoptosis, such as high-dose IVIg, may provide added benefit over supportive care alone.



Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)²

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, acute & life-threatening mucocutaneous diseases that are nearly always drug-related.

Epidemiology: Rare disease with high mortality (20-30%) that affects mainly adults, but may occur in all age groups. Both sexes are affected.

Etiology and pathogenesis

Predisposing factors:

1. Slow acetylator genotypes.
 2. Immunocompromised patients (e.g. HIV infection: Risk of developing TEN is 1000-fold higher, lymphoma).
 3. Concomitant administration of radiotherapy & anticonvulsants (most commonly, those with brain tumors).
 4. Genetic susceptibility.
- Drug metabolites formed in the skin mediate the necrolysis.
 - Humoral immune mechanisms: Evidenced by immunoreactant deposition in DIF.
 - CMI mechanisms: Supported by its association with GVHD & presence of inflammatory infiltrate.

Causes of SJS & TEN

- Drugs: The most common cause (80% of cases); Sulfonamides, phenytoin, phenylbutazone, allopurinol, ampicillin, NSAIDs.
- GVHD.
- Infections, e.g. Herpes virus.
- Neoplasms, e.g. Hodgkin's leukemia.
- SLE.
- Idiopathic.

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis

(TEN) are variants within a continuous spectrum of adverse drug reactions, whereas erythema multiforme (EM) is a distinct disorder with different clinical signs & precipitating factors.

The current model for the pathogenesis of SJS/TEN:

- Upon exposure to certain types of drugs, an individual with particular predisposing factors mounts a specific immune reaction to the drug or one of its metabolites.
- As a result of an interplay of cell types & cytokines, there is a strong expression of the cytolytic molecule FasL on keratinocytes as well as granulysin secretion from cytotoxic T-lymphocytes and natural killer cells.
- This leads to FasL- & granulysin-mediated apoptosis of keratinocytes and subsequent epidermal necrosis and detachment.
- Indeed, the apoptotic state of cells is transient in nature, and it is followed by necrosis if the apoptotic cells are not rapidly phagocytosed. In SJS and TEN, within hours, keratinocyte apoptosis becomes very abundant in lesional skin, thus rapidly overwhelming the phagocytic capacity of the affected skin.

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- Complete healing takes place without scarring over 2 weeks. Healing occurs by re-epithelialization from proliferation and migration of keratinocytes from 'reservoir' sites, such as healthy epidermis surrounding denuded areas and hair follicles within the areas of detachment. Scarring of skin, mucosal surface as the conjunctivae and nails occurs with 2ry bacterial infection.



Fig. 17. Stevens-Johnson syndrome



Fig. 18. Stevens-Johnson syndrome



Fig. 19. Toxic epidermal necrolysis

Clinical features that distinguish Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and SJS-TEN overlap

Clinical entity	SJS	SJS-TEN	TEN
Primary lesions	- Dusky &/or dusky red lesions. - Flat atypical targets.		- Poorly delineated erythematous plaques. - Epidermal detachment-spontaneous or by friction. - Dusky red lesions. - Flat atypical targets.
Distribution	- Isolated lesions - Confluence (+) on face & trunk.	- Isolated lesions - Confluence (++) on face & trunk.	- Isolated lesions (rare). - Confluence (+++) on face, trunk & elsewhere.
Mucosal involvement	Yes		
Systemic symptoms	Usually	Always	
Detachment (% BSA)	<10	10-30	>30

Adapted from: Bolognia et al., *Dermatology Textbook*, third edition, 2012.

How soon after starting a drug does TEN develop?

Most cases of TEN start 1-3 weeks after starting the drug. Phenytoin is an exception, requiring 2-8 weeks. If the patient had a similar eruption in the past, the time interval drops to <48 hours.

Complications

- Systemic complications:** Acute tubular necrosis, glomerulonephritis, bronchopneumonia, GIT bleeding & hemodynamic shock.
- Imperfect healing:**
 - Eye: Symblepharon, conjunctival synechiae, entropion, ingrowth of eyelashes.
 - Skin: Cutaneous scarring, irregular pigmentation, eruptive melanocytic nevi.
 - Mucous membrane: Persistent erosions of the mucous membranes, phimosis, vaginal synechiae.
 - Nail dystrophy and diffuse hair loss.
- Mortality rate:** 25-70%. Main causes of death are:
 - Infections (*S. aureus* and *Pseudomonas aeruginosa*).
 - Massive transepidermal fluid loss associated with electrolyte imbalance.
 - Inhibition of insulin secretion, insulin resistance, and onset of a hypercatabolic state.
 - Adult respiratory distress syndrome and multiple organ failure.

SCORTEN

HL

It represents a prognostic scoring system for patients with toxic epidermal necrolysis. The score is based upon the number of prognostic factors in a particular patient.

Prognostic factors	Points
Age > 40 years	1
Heart rate >120 bpm	1
Cancer or hematologic malignancy	1
BSA involved on day 1 above 10%	1
Serum urea level (>10 mmol/l)	1
Serum bicarbonate level (<20 mmol/l)	1
Serum glucose level (>14 mmol/l)	1
SCORTEN	Mortality rate (%)
0-1	3.2
2	12.1
3	35.8
4	58.3
≥5	90

BSA: body surface area.

Adapted from: Bolognia et al., *Dermatology Textbook*, third edition, 2012.

Histopathology (Figs 20, 21): As erythema multiforme with extensive eosinophilic necrosis of the epidermis and a cleavage plane above the basement membrane with a very little inflammation in the dermis, a feature that was later referred to as '**dermal silence**'.

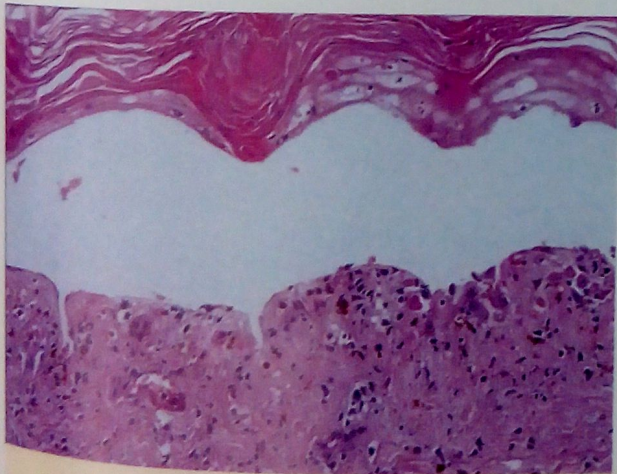


Fig. 20. Histopathology of TEN

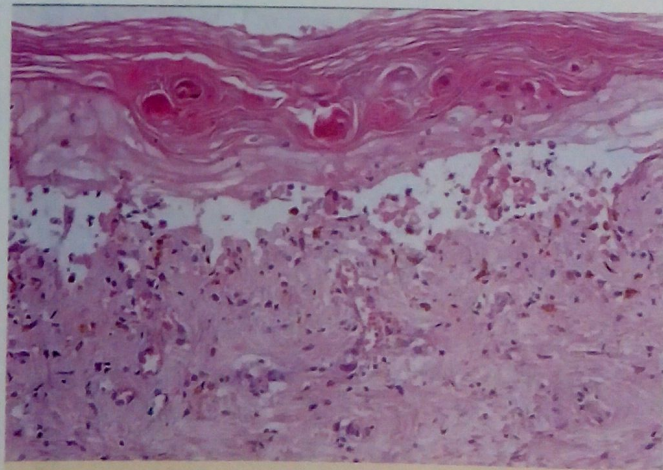


Fig. 21. Histopathology of TEN

DD: From SSS syndrome.

Treatment: In intensive care units or in burn units.

1. Supportive care:

- Hydration and nutritional support.
- Use of a controlled pressure thermoregulated bed and an aluminum survival sheet, instead of a regular bed and sheets, is recommended.

- Careful daily wound care:
 - Once daily.
 - Manipulated as little as possible.
 - Covered with vaseline gauze or silicone dressing until re-epithelialization occurs.
 - Non-detached areas are kept dry and not manipulated.
 - For the face, eyes, nostrils, mouth and anogenital region and interdigital: Cleansed daily with isotonic sterile sodium chloride solution+ antibiotic ointment or antiseptic solutions.
2. **Specific treatment:** No specific therapies:
- Cyclosporine (3-4 mg/kg/day).
 - Cyclophosphamide (100-300 mg/day).
 - Plasmapheresis, and N-acetylcysteine (2 g/6h).
 - Systemic corticosteroids have been the mainstay of therapy for decades, but their use remains controversial, despite a recent study suggesting efficacy when administered over a short period of time as pulse therapy.
 - IVIg contain antibodies against Fas that are able to block the binding of FasL to Fas. 1g/kg/day of IVIg for three consecutive days, thus giving a total dose of 3 g/kg.

Erythema Toxicum Neonatorum

Asymptomatic, generalized eruption affecting about 50% of the newborns. Onset is in the first 3 days of life in 90% of the cases and is extremely rare at birth. It resolves within 2-3 days without pigmentation.

Clinically: It consists of generalized erythematous macules, papules, large irregular areas of erythema and occasionally pustules. Almost always spares the palms and soles. There is eosinophilia in blood and tissue.

Histopathology: There is mild edema & perivascular and interstitial infiltrate mainly of eosinophils. The pustules are intrafollicular subcorneal containing mainly eosinophils.

DD: Transient neonatal pustular melanosis: It occurs in black infants, always at birth, as pigmented macules, vesicopustules, or ruptured vesiculopustules with a typical collarette of scale. It may last 3 weeks. There are intra- or subcorneal neutrophilic pustules with no local or blood eosinophilia.

Causes of neonatal vesiculopustular eruptions

Non-infectious group

• Benign:

- Erythema toxicum neonatorum.
- Transient neonatal pustular melanosis.
- Miliaria.
- Infantile acropustulosis.
- Eosinophilic pustular folliculitis.

• Potentially serious:

- Acrodermatitis enteropathica.
- Epidermolytic ichthyosis.
- Epidermolysis bullosa (EBS, JEB and RDEB).
- Neonatal herpes gestationis.
- Incontinentia pigmenti (vesicular phase).
- Neonatal pemphigus.
- Mastocytosis.

Infectious group

• Mild:

- Neonatal candidiasis.
- Impetigo neonatorum.
- Neonatal scabies.

• Serious:

- Bacterial infections:
 - Neonatal sepsis.
 - Neonatal listeriosis.
 - SSSS.
 - Necrotizing fasciitis.
 - Congenital syphilis.
- Congenital neonatorum.
- Viral infections:
 - Congenital CMV.
 - HSV.
 - VZV.

Miscellaneous

- Langerhan's cell histiocytosis.
- Neonatal acne.
- Neonatal Behçet's.
- Congenital TB.
- Neonatal hyper-IgE.
- Congenital erosive & vesicular dermatosis.
- Neonatal cutaneous aspergillosis.
- Neonatal pustular psoriasis.
- Congenital porphyria.

Figurate Erythemas



- In figurate erythemas, the lesions have an annular, arciform or polycyclic appearance.
- Wide range of cutaneous diseases can have an annular configuration.

• There are four "classic" figurate erythemas:

1. ***Erythema annulare centrifugum***

- Erythematous annular lesions that migrate centrifugally.
- Although often idiopathic in nature, it can be associated with infections (e.g. tinea pedis) & anecdotally with other disorders or exposures.

2. ***Erythema marginatum (rheumaticum)***

- Cutaneous manifestation of acute rheumatic fever.
- Associated findings include carditis, migratory polyarthritis, Sydenham's chorea & subcutaneous nodules.

3. ***Erythema (chronicum) migrans***

- The initial cutaneous manifestation of Lyme disease and is seen in 60–90% of patients diagnosed with the disease.

4. ***Erythema gyratum repens***

- Composed of concentric rings with a wood-grain appearance.
- It represents a paraneoplastic phenomenon & the most common underlying neoplasm is carcinoma of the lung.



Figurate Erythemas ¹

Four 'classic' figurate erythemas:

- Erythema annulare centrifugum.
- Erythema (chronicum) migrans.
- Erythema gyratum repens.
- Erythema marginatum (rheumaticum).

Differential diagnosis of figurate erythema

HL

Transient lesions (typically lasting <24 hrs)	• Urticaria. • Erythema marginatum. • Erythema marginatum-like lesions of hereditary angioedema. • African trypanosomiasis. • Erythrokeratoderma variabilis.
Urticarial lesions lasting >24 hrs	• Allergic urticarial eruption. • Annular erythema of infancy. • Wells' syndrome. • Urticarial vasculitis. • Erythema migrans. • Erythema annulare centrifugum (deep). • Lymphocytic infiltration of Jessner. • LE tumidus. • Annular erythema of Sjögren's syndrome.
Granulomatous lesions	• Granuloma annulare, sarcoidosis. • Interstitial granulomatous dermatitis (IGD), interstitial granulomatous drug reaction (IGDR). • Borderline or tuberculoid leprosy.
Papulosquamous lesions	• Psoriasis, lichen planus, pityriasis rosea. • Erythema annulare centrifugum (superficial). • Erythema gyratum repens. • Tinea corporis. • Annular LE (subacute>discoid), neonatal LE. • Seborrheic dermatitis. • Ichthyosis linearis circumflexa of Netherton syndrome.
Lesions with absence or variable presence of scale	• Annular lichenoid dermatitis of youth (red-brown plaques with central hypopigmentation, on flanks). • Secondary syphilis. • Mycosis fungoides.
Pustular lesions	• Pustular psoriasis (annular pattern). • Sneddon-Wilkinson disease, IgA pemphigus. • Eosinophilic pustular folliculitis (Ofuji's disease).
Erosive/vesiculobullous lesions	• EM, SJS. • Necrolytic migratory erythema. • Bullous pemphigoid, gestational pemphigoid. • Linear IgA bullous dermatosis. • EBS (especially Dowling-Meara subtype). • Annular epidermolytic ichthyosis.
Purpuric lesions	• Purpura annularis telangiectoides. • Acute hemorrhagic edema of infancy.
Perforating lesions	• Elastosis perforans serpiginosa.

1) Erythema Annulare Centrifugum "EAC"

There are multiple annular or serpiginous lesions with raised, red, firm border, that expand peripherally forming arciform segments (Figs 22-26). The commonest sites are the buttocks, thighs and trunk. The lesions may last over many years.

Once the other three major figurate erythemas (with specific etiologies) and the other causes of figurate erythemas are excluded, EAC often becomes a 'default' diagnosis.



Fig. 22. Erythema annulare centrifugum



Fig. 23. Erythema annulare centrifugum



Fig. 24. Erythema annulare centrifugum



Fig. 25. Erythema annulare centrifugum



Fig. 26. Erythema annulare centrifugum

the superficial form: Shows less induration with scaling along the gyrate border.

Histopathology: Perivascular "coat-sleeve-like" infiltrate of mononuclear cells mainly lymphocytes in middle and lower dermis. There is no epidermal changes. In the superficial form, there is epidermal changes; spongiosis, acanthosis and parakeratosis.

Etiology: Usually unknown, but may be 2ry to fungus infection, drug sensitivity, underlying malignancy, liver diseases or Sjögren's syndrome.

Treatment (Fig. 27): Topical steroids, TCI, calcipotriol or antipruritic agents.



Fig. 27. Erythema annulare centrifugum before & after treatment with topical steroids & oral antihistamines

ii) Erythema chronicum migrans "ECM" – Lyme disease (see chapter 2, page 60).

III) Erythema gyratum repens "EGR" (Fig. 28)

Generalized eruption of parallel erythematous bands with an annular and serpiginous arrangement with peripheral scaling resembling the grain of wood. The lesions migrate about 1 cm/day, frequently.

Almost all reported cases have been associated with carcinoma usually of the lung (the most common) or breast. EGR usually resolve with complete removal of the underlying tumor.

Histopathology: Non-specific, mild perivascular mononuclear infiltrate.

IV) Erythema marginatum rheumaticum "EMR"

- It occurs in 10% of patients with active rheumatic fever, more in children and usually associated with cardiac affection. It consists of asymptomatic, non-scaly, pale or red rings that may produce polycyclic pattern and fades in few hours or 2-3 days.
- Associated findings include carditis, migratory polyarthritis, Sydenham's chorea and subcutaneous nodules.

Pathogenesis

HL

- Abnormal humoral and cellular immune response to one or more antigens associated with group A β -hemolytic streptococci (e.g. M protein).
- Antigenic mimicry may play a role in that epitopes cross-reacting with group A streptococcal antigens have been identified in human myosin, actin, tropomyosin, keratin, laminin, N-acetylglucosamine, and vimentin.

Eosinophilic cellulitis "Wells' syndrome, 1971"

It is characterized by a cellulitis-like picture clinically and tissue eosinophilia, edema and "flame figures" histologically.

It may represent a tissue reaction to various stimuli including myeloproliferative disorders, infections/infestations "including dermatophytes, viruses and *Toxocara canis*", insect bites or stings, and drugs. The eosinophils mediate the tissue injury through the release of major basic protein. More recently, peripheral lymphocytes isolated from patients with Wells' syndrome were reported to have exaggerated responses to mosquito salivary gland extracts.

Clinically: There are recurrent episodes of sudden onset of erythematous cellulitis-like swellings that often are painful or pruritic, but in contrast to bacterial cellulitis, are not warm. Some blistering may be present. Within 2-3 days, the erythema and edema are replaced by greenish-blue induration that requires 6-8 weeks to resolve, without scarring. Fever and blood eosinophilia may be present.

Histopathology

- Marked dermal edema and dense cellular infiltrate composed predominantly of eosinophils. The infiltrate extends into the subcutaneous tissue and may even extend into the underlying muscle.



Fig. 28. Erythema gyratum repens

What are "Flame figures"?

- Lesions from 1 to 3 weeks old show, in addition to eosinophils, elongated areas of fibrinoid necrosis of the dermal collagen surrounded by eosinophils and histiocytes referred to as flame figures.
- These flame figures are a hallmark of Wells' syndrome, but they are not specific. Other diseases featuring flame figures include arthropod bites and stings (namely ticks, bees, fleas and spiders), mastocytomas, scabies and other parasitic infestations, prurigo nodularis, eczema and dermatophyte infections.
- Vasculitis of dermal vessels is not seen.

Treatment

- Oral corticosteroids, typically prednisone (10-80 mg daily) tapered over 1 month.
- Other lines: Cyclosporine (1.25-2.5 mg/kg/day), minocycline, colchicine, antimalarials, dapsone, griseofulvin, interferon- α and antihistamines.
- For mild cases: Potent topical corticosteroids.

Telangiectasias



- Telangiectasia is due to persistently dilated dermal vessels and not angiogenesis.
- Individual vessels can be discerned and range in color from light red to deep purple and will usually empty with pressure.
- Can occur as a primary process, a result of cutaneous damage, or secondary to systemic disease.
- Treatment is often not required; however, options include cosmetic camouflage, light or fine wire diathermy, injection sclerotherapy, and laser or intense pulsed light therapies.

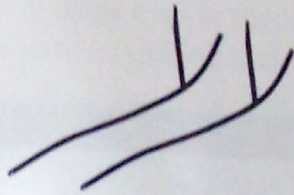


Telangiectasia

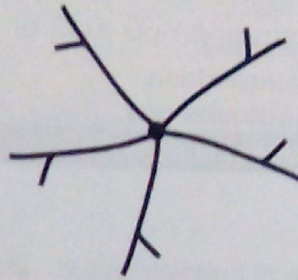
Telangiectasias are permanently dilated, small vessels (Fig. 29). They appear as dull red, linear, arborized, spider, or punctate markings.



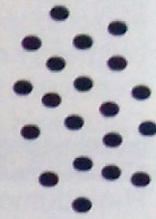
1) Linear



2) Arborized



3) Spider



4) Punctate

Telangiectasia occur as a result of vascular dilation rather than new vessel growth and are thought to arise from capillaries, venules or small arteriovenous malformations.



Fig. 29. Telangiectasia

Causes of telangiectasia

Primary

- Spider telangiectasias (also associated with estrogen excess).
- Hereditary benign telangiectasia*.
- Angioma serpiginosum.
- Unilateral nevoid telangiectasia.
- Generalized essential telangiectasia.
- Cutaneous collagenous vasculopathy.

Secondary to physical changes or damage

- Photodamage.
- Post-radiation therapy.
- Traumatic.
- Venous hypertension.

Skin disease

- Telangiectatic rosacea.
- Incipient or involuted infantile hemangiomas.

Hormonal/metabolic

- Estrogen-related:
 - Liver disease.
 - Pregnancy.
 - Exogenous estrogens.
- Corticosteroids.

Systemic conditions

- Carcinoid syndrome.
- Mastocytosis (telangiectasia macularis eruptiva perstans).
- Autoimmune connective tissue diseases:
 - Lupus erythematosus.
 - Dermatomyositis (Fig. 30).
 - CREST syndrome/systemic sclerosis.
- Mycosis fungoides, including poikilodermatous
- B-cell lymphomas.
- Angiolupoid sarcoidosis.
- GVHD (in the context of poikiloderma).
- HIV infection (anterior chest).

Congenital malformations & genodermatoses

- Cutis marmorata telangiectatica congenita.
- Klippel-Trenaunay syndrome.
- Hereditary hemorrhagic telangiectasia syndrome.
- Ataxia-telangiectasia.
- Hypotrichosis-lymphedema-telangiectasia syndrome.
- Rombo syndrome.
- Bloom syndrome.
- Rothmund-Thomson syndrome.
- Poikiloderma with neutropenia.
- Dyskeratosis congenita.
- Xeroderma pigmentosum.
- Goltz syndrome (in Blaschko's lines).
- GM1-gangliosidosis (also associated with angiokeratoma corporis diffusum).
- Prolidase deficiency.



Fig. 30. Periungual telangiectasia with ragged cuticle in dermatomyositis

* Childhood onset of multiple punctate, linear or arborizing telangiectasias favoring sun-exposed areas of the face & upper extremities; the vermillion lips & palate are occasionally affected, but there is no visceral involvement.

Ataxia telangiectasia "Louis Bar syndrome"

It is a rare syndrome with autosomal recessive inheritances.

Pathogenesis

- Mutations in ataxia-telangiectasia mutated (ATM) gene, which encodes (kinases) that play a central role in activating apoptosis in responses to DNA damage causing defective excision repair of DNA and sensitivity to ionizing radiation.
- Immunological abnormalities, e.g. IgA, IgE & IgG deficiency, CMI defects, thymic abnormalities, lymphopenia.

Clinical picture

- **Progressive cerebellar ataxia** (the 1st manifestation), usually evident in early infancy.
- **Skin manifestations:**
 - Telangiectasia starts in bulbar conjunctivae then affects ears, eyelids, face and buttocks. It develops at a median age of 6 years.
 - Other skin manifestations: Progressive progeric changes of the skin and hair, non-infectious cutaneous granulomas, poikiloderma, eczematous dermatitis, seborrheic dermatitis and keratosis pilaris.
 - BCC during the third decade of life.
- **Other systemic manifestations:**
 - Recurrent pulmonary infections.
 - Insulin resistance and DM.
 - Malignant lymphoma may develop later in life and there is ↑ breast cancer.

Treatment

- Supportive treatment: Avoidance of sun exposure and use of sunscreens, antibiotics for infections and physical therapy for patients with neurologic dysfunction.
- Radiation & radiomimetic chemotherapeutic agents, especially bleomycin, should be avoided.
- Recently: ATM gene function could be increased by treatment with aminoglycosides.

Angioma serpiginosum

It is a nevroid disorder of small blood vessels of upper dermis occurring mainly in females.

There are red, non-palpable puncta that are grouped closely together in a macular or net-like pattern mainly in lower extremities. Irregular peripheral spread creates the characteristic serpiginous border.

Methods for treating telangiectasias

- **Electrosurgery:**
 - Electrodesiccation.
 - Timed diathermocoagulation.
- **Laser:**
 - Argon.
 - Carbon dioxide.
 - Tunable dye.
- **Dermabrasion**
- **Medical:**
 - Tetracycline: For generalized essential telangiectasia.
 - Estrogen: For hereditary hemorrhagic telangiectasia.
- **Sclerotherapy**, e.g. Na morrhuate, hypertonic saline:
 - Intradermal.
 - Intravascular.

Spider Telangiectasia

- Synonyms: Nevus araneus – Spider nevus – Spider angioma.
- Slightly raised central red papule (central feeding arterial vessel) and multiple small, radiating, dilated vessels.
- They are commonly located on the face, neck, upper trunk and hands (Figs 31, 32).
- They are usually seen in otherwise healthy individuals (especially women and children).
- Multiple lesions commonly occur with pregnancy, liver disease and oral contraceptive pills (OCPs).
- Spontaneous resolution may occur, especially after pregnancy.
- Treatment options include electrosurgery or vascular lasers.



Fig. 31*. Spider angioma



Fig. 32**. Spider angioma

Generalized Essential Telangiectasia

- Widespread and progressive telangiectasia.
- Adult women but may commence in childhood.
- Legs, but trunk may be involved at a later stage.

Hereditary Hemorrhagic Telangiectasia HL

Osler-Weber-Rendu disease

- AD due to mutations in at least two different genes (to date, HHT1 and HHT2), which encode endoglin and activin receptor-like kinase 1 (ALK-1), respectively. Both of these glycoproteins are TGF- β receptors expressed by vascular endothelium, and they are thought to play a role in angiogenesis and vessel wall integrity.
- Multiple telangiectasias (which are actually arteriovenous malformations) which increase in size and number with age are seen in:
 - Skin: Appear after puberty or even later in life – on the face, hands and fingertips.

* Dermatology, illustrated study guide & comprehensive board review, 2012.

**Bolognia et al., Dermatology Textbook, Third edition, 2012.

- Mucous membrane: First seen during adolescence.
- GIT: Obvious hemorrhage or iron deficiency.
- Visceral involvement (lung, liver and CNS): Hemorrhage and paradoxical emboli.

The diagnosis may first be suspected in children who have repeated episodes of epistaxis; however, the initial presentation may be during the second or third decades.

Treatment

- Skin: Diathermy, cautery or laser may be used to treat individual lesions.
- Surgical management or embolization may be required for uncontrolled hemorrhage from mucosal lesions or complications arising from visceral lesions.

Erythromelalgia HL

- Episodic condition characterized by a burning sensation, erythema and increased skin temperature affecting acral sites, particularly the lower extremities.
- Precipitated by heat and relieved by cooling.
- May be idiopathic, familial or arise secondarily due to an underlying condition (e.g. thrombocythemia).

3 major forms are present:

- **Type 1:** Associated with thrombocythemia.
- **Type 2:** Primary or idiopathic form.
- **Type 3:** Associated with underlying causes other than thrombocythemia (myelodysplastic syndromes, diabetes mellitus, peripheral vascular disease, vasculitis, systemic lupus erythematosus and other autoimmune CTDs).

Treatment

- Cooling and elevation of the legs during the attacks.
- Analgesia (Aspirin can be effective for type 1).
- Topical therapies: 10% capsaicin and lidocaine patches.
- Oral medications: SSRIs, tricyclic antidepressants, anticonvulsants, calcium channel blockers and the prostaglandin analogue misoprostol.
- IV: Nitroprusside, prostaglandin E1, and lidocaine (combined with oral mexiletine).
- More invasive approaches include epidural infusions of bupivacaine and opiates.
- Lumbar sympathetic blocks and bilateral lumbar sympathectomies.

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